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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/253,573	02/19/99	CHEN H	99.001

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EXAMINER	
SCHNIZER, R	
ART UNIT	**PAPER NUMBER**
1632	7

DATE MAILED: 07/17/00

Please find below and/or attached an Office communication concerning this application r proceeding.

Commissioner of Patents and Trademarks

FILE COPY

Office Action Summary	Application No. 09/253,573	Applicant(s) Chen
	Examiner Richard Schnizer	Group Art Unit 1632

☒ Responsive to communication(s) filed on *Apr 21, 2000*

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is clos d** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-29* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-29* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

An amendment and response to restriction requirement was received and entered as Paper No. 6 on 4/21/2000.

Election/Restriction

Applicant's election with traverse of group I in Paper No. 6 is acknowledged. The traversal is on the ground(s) that the inventions are not independent. This is not found persuasive. Applicant's interpretation of the meaning of "independent and distinct" is inconsistent with that set forth at MPEP 802.01. Applicant has admitted that groups I and II are distinct. See page 5 of Paper No. 6. Therefore, the requirement is still deemed proper and is therefore made FINAL.

Claims 30-43 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 5.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 1-29 under 35 U.S.C. 112, first paragraph is withdrawn in view of Applicant's statement in Paper No. 6 that the claimed invention is not intended to be used for gene therapy. It is noted that Applicant did not rebut the grounds of rejection with respect to enablement of gene therapy. See page 8 of Paper No. 6, last sentence of fourth paragraph.

Claims 10 and 24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 10 and 24 are directed to a method of inducing the rupture of red blood cells *in vivo* by genetic mutation.

The specification teaches that the life cycle of red blood cells can be modified by genetic mutation but teaches no mutations which would be suitable for this purpose, and provides no guidance as to how to obtain cells comprising these mutations. Applicant has submitted references to support the position that natural mutations resulting in shortened red blood cell life time were well known in the art at the time of filing. See Paper No. 6. However, Applicant has not made any such cells available, made available mutated genes which would be required to generate such cells, or provided any guidance whatsoever in the process of generating the cells. Relevant to these issues, the court found in Genentech Inc. v Novo Nordisk A/S, that when the

specification omits any specific starting material required to practice an invention, there is a failure to meet the enablement requirement. See 42 USPQ2d 1001.

> It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See , e.g. , Hybritech Inc. v. Monoclonal Antibodies, Inc. , 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

Because the specification has failed to teach how to obtain the basic starting materials required for the invention, one of skill in the art would have to perform undue experimentation in order to practice the claimed invention as intended.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 10 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are those involved in introduction of the genetic mutation

into the cell. Applicant has failed to describe which mutations would be introduced into the cells and how. In Paper No. 6, Applicant submitted a paper by Jacobasch and Rapoport which lists a variety of mutations which can cause early lysis of red blood cells. See Table 4 on page 145. However, claims 10 and 24 recite none of the essential steps required for engineering a mutation into an isolated cell. Furthermore, only one of these mutations is an autosomal dominant mutation. In order to use the recessive mutations, Applicant would ostensibly need to perform targeted replacement of the both wild type alleles of a target cell with mutated copies in order to achieve the desired effect. It is noted that the specification discloses none of the requisite teachings, so any attempt to incorporate the required method steps would constitute the introduction of new matter.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5, 8, 9, 16-18, 22, 23, and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Hollis et al (US Patent 5,538,885, issued 7/23/96) .

Hollis teaches a method of obtaining red blood cell progenitors from an animal, transfecting them with a vector comprising a gene of interest under the control of either a

hemoglobin promoter and enhancer, or a PLA2 promoter, and reintroducing the cells into the individual. The encoded protein may be a hormone or an enzyme, and the protein may be retained intracellularly or secreted. Hollis does not teach that the red blood cells should lyse and release the protein into the blood. However, lysis of red blood cells is an inherent property, therefore Hollis anticipates the claims. See entire document, especially abstract; column 2 lines 7-17; column 3, lines 18-22 and 58-61; sentence bridging columns 6 and 7; column 7, lines 24-47; column 8, lines 18-24; Example 2, column 13, line 47 to column 14, line 9; and Example 6, column 16, line 56 to column 17, line 40.

It is noted that while the disclosure of Hollis is enabling for the expression of proteins *in vivo*, it is not enabling for gene therapy. With respect to claim 5, it is noted that all mammalian promoters are native to red blood cells.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, 16, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hollis et al (US Patent 5,576,206, issued 11/19/96), Rixon et al (Mol. Cell. Biol. 8(2): 713-721, 1988), and Zhang et al (Shengwu Huaxue Zazhi 11(3): 343-347, 1995).

The invention is a method of producing and delivering a protein *in vivo*. The protein is produced by transfecting red blood cell precursors with an expression vector *ex vivo*, engrafting the transfected cells, allowing them to express the protein as they differentiate into red blood cells, and allowing the red blood cells to eventually lyse, releasing the protein into the blood. The vector may comprise an enhancer, a hemoglobin promoter, a mutated promoter, or a mutated hemoglobin promoter, and it may be delivered by a lentiviral vector.

Hollis teaches a method of obtaining red blood cell progenitors from an animal, transfecting them with a vector comprising a gene of interest under the control of either a hemoglobin promoter and enhancer, or a PLA2 promoter, and reintroducing the cells into the individual. Hollis does not teach the use of a mutated promoter.

Rixon teaches a mutated hemoglobin promoter having increased activity relative to the wild type. See entire abstract, particularly the third and last sentences.

Zhang suggests the transfer of an expression cassette, comprising the promoter of Rixon, into hematopoeitic stem cells. See last sentence of abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use a mutated hemoglobin promoter in the invention of Hollis. One would have been motivated to do so, because Rixon teaches a mutated hemoglobin promoter with enhanced transcriptional activity, and Zhang suggests the use of this promoter to drive expression of proteins in hematopoietic stem cells.

Thus the invention as a whole was *prima facie* obvious.

Claims 1, 6, 7, 16, 20, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hollis et al (US Patent 5,576,206, issued 11/19/96), Schlegel (US Patent 5,576,206, issued 11/19/96), and Wickham et al (US Patent 5,846,782, issued 12/8/98).

The invention is a method of producing and delivering a protein *in vivo*. The protein is encoded by a viral vector which may be an adenoviral vector or a retroviral vector, and more specifically, a lentiviral vector.

Hollis teaches a method of obtaining red blood cell progenitors from an animal, transfecting them with a vector comprising a gene of interest under the control of either a hemoglobin promoter and enhancer, or a PLA2 promoter, and reintroducing the cells into the individual. Hollis teaches that the vector can be any recombinant DNA material capable of transferring DNA from one cell to another. See column 3, lines 58-61. Hollis does not specifically teach the use of viral vectors.

Schlegel teaches a method of obtaining red blood cell progenitors from an individual, transfecting them with a retroviral or adenoviral vector comprising a gene of interest under the control of an actin promoter, and reintroducing the cells into the individual. See column 3, lines 22-36; column 5, lines 10, and 62-64; column 7 lines 6-15.

Wickham teaches that lentiviruses are useful for gene transfer to hematopoietic cells. See column 11, lines 52-55; column 12, lines 29-31, and 41-44; and column 19, lines 14-18.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use an adenoviral, retroviral or lentiviral vector in the invention of Hollis. One would have

been motivated to do so because Schlegel teaches that adenoviral and retroviral vectors can be used to transfect red blood cell precursors, and because Wickham demonstrates that lentiviral vectors are useful for gene transfer to hematopoietic cells.

Thus the invention as a whole was *prima facie* obvious.

Claims 1, 11-16, 25, and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hollis et al (US Patent 5,576,206, issued 11/19/96), Schlegel (US Patent 5,576,206, issued 11/19/96), and Chatterjee et al (US Patent 5935821, filed 11/21/96).

Hollis teaches a method of obtaining red blood cell progenitors from an animal, transfecting them with an expression vector comprising a gene of interest, and reintroducing the cells into the individual. Hollis teaches that the gene of interest can be any gene encoding a polypeptide, including human growth hormone, and phospholipase A2. See column 2, lines 44-52, and Example 2, column 13, line 47 to column 14, line 9; and Example 6, column 16, line 56 to column 17, line 40. Hollis does not teach the expression of a cofactor, an antibody an interferon, a fusion protein, a mutated protein, or a peptide.

Schlegel teaches a method of obtaining red blood cell progenitors from an individual, transfecting them with a retroviral or adenoviral vector comprising a gene of interest, and reintroducing the cells into the individual. The gene of interest may be an enzyme (Factor IX), a cofactor (Factor VIII), an interferon, or a hormone. See column 9, lines 10, 34, 40, and 44-47.

Chatterjee teaches genetic immunization by delivery and expression of nucleic acids encoding an antibody, or peptides or fusion proteins thereof. See column 4, lines 59-64; and column 23, lines 25-30; column 24, lines 5-9.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the system of Hollis to express a cofactor, an antibody, an interferon, a fusion protein, a mutated protein, or a peptide. In this respect, a peptide or a truncated portion of a protein can be viewed as a mutated protein. One would have been motivated to express a cofactor or an interferon because Hollis teaches that any heterologous protein may be expressed in the system, and Schlegel suggests expressing a cofactor or an interferon in red blood cell progenitors *in vivo.* Furthermore, Chatterjee suggests genetic immunization by expression in vivo of polynucleotides encoding either an antibody, fusion proteins comprising the antibody, or pentapeptides derived from the antibody. Also Chatterjee teaches that the polynucleotides may be delivered to peripheral blood cells for ongoing secretion of the protein of interest. The method of Hollis would facilitate such extended expression.

Thus the invention as a whole was *prima facie* obvious.

Response to Arguments

Applicant's arguments filed 4/21/2000 have been fully considered as they apply to the current grounds of rejection, but they are not persuasive.

Applicant raises two central arguments. First, the cited art does not teach the production of a protein of interest wherein the production is limited to progenitor cells of red blood cells. Second, the cited art does not teach protein delivery by rupture of red blood cells.

Hollis teaches the expression of a protein of interest in only the progenitor cells of red blood cells. This is achieved in two ways. First, Hollis teaches the use of a hemoglobin promoter/enhancer to which restricts expression to red blood cell progenitors. This allows one to use stem cells, which can differentiate into lymphocytes as well red blood cells, while still limiting gene expression to red blood cell precursors. Second, Hollis teaches the use of erythroid leukemia cell originally isolated from rat, mouse or human individuals. This embodiment allows the use of promoters which are active in a variety of cells, while limiting expression of the gene of interest to red blood cell precursors.

Applicant's argument concerning protein delivery by rupture of red blood cells are unconvincing because Applicant has provided no evidence that protein expressed in red blood cell precursors would not be released by later rupture of the red cells. Cell rupture is an inherent characteristic of red blood cells, as pointed out by Applicant at page 9, lines 13-16 of the specification. Any protein comprised by the cell would reasonably be expected to be released by cellular rupture. Hollis teaches that heterologous proteins may be produced in red blood cell precursors for secretion or for intracellular deposition. See column 3, lines 18-22. In either case, some of the expressed protein can be expected to be released upon cellular rupture. Applicant argues that the cited art does not recognize that the rupture of the cells can be taken advantage of

for the purpose of delivery, however recognition of inherent qualities is not required in order for a reference to be anticipatory.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday-Friday from 7:30 to 4:00 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached at 703-308-2035. The FAX phone number for art unit 1632 is 703-308-0294.

Inquiries of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Richard Schnizer, Ph. D.

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER